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PARFOMAK, ANDREW N. 875 THIRD AVE, 8TH FLOOR NEW YORK, NY 10022			EXAMINER LONG, SCOTT	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/538,038	Applicant(s) SLACK ET AL.	
	Examiner SCOTT LONG	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-13,18-26 and 28-39 is/are pending in the application.
- 4a) Of the above claim(s) 35,36,38 and 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1,6-13,18-26,28-34 and 37 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 13 August 2009.

Election/Restrictions

Newly submitted claims 35-36 and 38-39 are directed to an species that are independent or distinct from the invention originally claimed (see reasoning below).

Since applicant has received an action on the merits for the originally presented invention (i.e., method comprising using a chimeric G-protein and the bitter taste receptor), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 35-36 and 38-39 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

This application contains claims directed to the following patentably distinct species:

- 1) methods comprising a sweet taste receptor (claims 35 and 38);
- 2) methods comprising a umami taste receptor (claims 36 and 39);
- 3) methods comprising a bitter taste receptor (claims 11 and 32).

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is

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finally held to be allowable. Currently, claims 12 and 33 are generic. The applicant has constructively elected by original presentation species #3 (methods comprising a bitter taste receptor (claims 11 and 32)).

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are

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added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Claim Status

Claims 1, 6-13, 18-26, and 28-39 are pending. Claims 35-39 are newly added. Claims 1, 11-13, 18, 21, 24, 32-34 are amended. Claims 2-5, 14-17 and claim 27 are cancelled. Claims 35-36 and 38-39 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 1, 6-13, 18-26, 28-34 and 37 are under current examination.

Priority

This application claims benefit as a 371 of PCT/CH03/00830 (filed 12/17/2003) which claims benefit of 60/434,790 (filed 12/18/2002). The instant application has been granted the benefit date, 18 December 2002, from the application 60/434,790.

RESPONSE TO ARGUMENTS

35 USC § 112, 1st and 2nd

The rejections of claims 1, 6-13, and 18-34 under 35 USC 112, 1st paragraph (new matter) and under 35 USC 112, 2nd paragraph are withdrawn in response to the applicant's claim amendments.

The applicant's claim amendments have been fully considered and are persuasive.

The applicant has amended the claims so that term "G15/gust44" has been changed to "G_{α15}/Gust44." Likewise the G16 terminology has been similarly amended. Furthermore, the applicant states that he interprets the examiner's rejection as a "nomenclature issue." The applicant has demonstrated (e.g., (Pronin et al., *Curr Biol.* 2007 Aug 21; 17(16): 1403-8) and (Sakurai et al. *J Agric Food Chem.* 2009 Mar 25; 57(6): 2508-14)) that the art refers to the claimed chimeric G-protein by the names "G_{α16Gust44}" and "G_{α16} Gust44." The applicant, therefore, indicates that he does not see the reasoning behind the new matter and indefiniteness rejections.

Although the examiner will try to better explain why the claim language is problematic, he will withdraw the rejection in order to focus on the art rejections.

The problem the examiner finds with the claim language is that the structure of the molecule is not clearly stated. The amended claim language creates a lack of clarity to the skilled artisan which the examiner believes could be introducing new matter. For example, the structure of the claimed molecule, as taught by the specification, is directed to a chimeric G_{α15}-protein or chimeric G_{α16}-protein having a C-terminus where the last 44 amino acids of Gustducin replace the last 44 amino acids of the G_{α15}-protein or G_{α16}-protein. However, the flowery language and confusing intermixing of terms describing the original G-protein and the newly created chimeric G_{α16}/Gust44 protein create ambiguity over the actual structure of the claimed molecule. In the previous rejections, the examiner was attempting to help the applicant clarify the language of the instant claims. The currently amended claims, like the previously rejected claims, seem to have replaced the last 44 amino acids of the chimeric G-protein with 44 amino acids of Gustducin. This is either redundant (since the chimeric G-protein already contains the Gust44 substitution) or inaccurate, since it was the original (non-chimeric) G-protein that has had the Gust44 substitution. The examiner will not permit the applicant through inexactly claimed subject matter to capture some new structures not taught by the specification. While the examiner prefers clearer claim language, he will accept that the applicant chooses to claim a given structure through inaccurately written claims. While the examiner does not view the problem as a “nomenclature issue,” he accepts that is the viewpoint of the applicant. For the sake of the art rejections, the examiner has

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interpreted the instant claims to mean "a chimeric G-protein comprising G_{α15} or G_{α16} wherein the 44 amino acid C-terminus of the G_{α15} or G_{α16} is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2."

Therefore, the examiner hereby withdraws the rejection of claims 1, 6-13, and 18-34 under 35 USC 112, 1st paragraph and under 35 USC 112, 2nd paragraph.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-13, 18-26 and 28-34 remain rejected under 35 U.S.C. 103(a) as being obvious over Margolskee (US-5,817,759, issued 6 October 1998) in view of Yao et al. (US-7,041,457, issued 9 May 2006) and further in view of Ruiz-Avila et al. (PNAS. July 17 2001. vol.98; No.15: 8868-8873) for the reasons of record and the comments below.

Applicant's arguments (Remarks, pages 8-24) and claim amendments have been fully considered but are not persuasive. The applicant indicates that the remarks on pages 9-14 are a summary of the arguments. Therefore, the examiner will view these remarks as being merely a preamble to the actual arguments which follow. Accordingly, no comments by the examiner seem necessary for the remarks on pages 9-14.

The applicant has submitted claim amendments to claims 1 and 18. The claim amendments further modify these claims by introducing the phrase, "where the chimeric protein, when employed in a mammalian cell-based assay increases the signal strength to at least double the signal strength of wild type Gα16. The applicant has argued that the amendments to the product claims provide a characteristic (i.e., enhanced signal strength) not recognized by the cited art (Remarks, page 16-18). The applicant also argues that this demonstrates unpredictability in the art. Contrary to the applicant's assertion, the product claims (i.e., claims 1-9, 18-26 and 28-30) are directed to a

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chimeric G-protein having a particular structure and nucleic acids encoding said chimeric G-protein. Particularly, the claims encompass a chimeric G-protein comprising $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the 44 amino acid C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2.

Amended claims 1 and 18 recite that "when employed in a mammalian cell-based assay increases the signal strength to at least double the signal strength of wild type $G_{\alpha 16}$."

The new claim amendments do not further limit the structure of the claimed chimeric protein. Therefore, these are merely intrinsic characteristics of the claimed structure under certain manipulated conditions. MPEP 2112.01 indicates that "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.' *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433."

The applicant has attempted to demonstrate that the prior art products do not necessarily possess the characteristics of the claimed product. Particularly, the applicant has argued that Ueda's chimeric G-protein, G16Gust5, does not work like the claimed G16Gust44 (remarks, page 24) and therefore the G16Gust5 molecule of Ueda

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would not provide a signal strength useful for screening (remarks, page 22). If the applicant has read the previous Action (filed 4/16/2009), he is well aware of the reasoning the examiner used to support his conclusion that the cited art suggests the structure of the claimed chimeric G- protein. The examiner has previously discussed post-filing art of Ueda, which is not among the art cited in the pending rejection.

The examiner believes that the applicant's representative is not furthering prosecution by reiterating previously addressed. As previously indicated (see Action, filed 4/16/2009): Ueda et al. (*Journal of Neuroscience*, Aug. 13, 2003; 23(19):7376-7380) teach chimeric G-proteins having $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ are replaced by several alternative C-terminal amino acids of Gustducin, including the terminal 5, 11, 37 and 44 amino acids. Ueda et al. teach that only the 37 and 44 C-terminal amino acids provide functional chimeric G-proteins. This is consistent with the teachings of Margolskee who teaches "the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical. The carboxyl terminal identity is of particular importance because it encompasses the site that has been implicated in G protein/receptor interactions" (col.9, lines 13-16, emphasis added by examiner). By pointing the only a single example, G16Gust5, and ignoring the example most like the claimed invention, G16Gust44, the applicant has chosen to ignore certain teachings that support the prima facie obviousness of the instant invention. This is merely spurious argument. The G16Gust44 provides evidence that the chimeric G-protein suggested by the art teaches the disputed characteristic (i.e.,

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increased signal strength). The examiner provided cited art that suggests a chimeric G-protein molecule having the terminal 44 amino acids of Gustducin, and did not formulate a rejection for a chimeric G-protein molecule having only the terminal 5 amino acids of Gustducin. Therefore, the applicant finds the applicant's argument unpersuasive.

The applicant further argues that the teachings of Ueda (not cited in the pending rejection) indicate unpredictability in the art (remarks, pages 15-17, Inherency argument). The applicant uses the teachings of Ueda regarding G16/gust5. The applicant suggests that because G16/gust5 does not produce a robust signal strength, there is no predictability or prima facie case of obviousness. As described above, Ueda teach chimeric G-proteins having $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ are replaced by several alternative C-terminal amino acids of Gustducin, including the terminal 5, 11, 37 and 44 amino acids. Ueda et al. teach that only the 37 and 44 C-terminal amino acids provide functional chimeric G-proteins. Ueda certainly show predictability of a chimeric G-protein having a C-terminal 44 amino acid substitution of gustducin. Ueda does not demonstrate unpredictability; rather Ueda demonstrated predictability, regarding the function of a C-terminal 44 amino acid substitution of gustducin in a chimeric G-protein. Therefore, the applicant finds the applicant's argument unpersuasive. The issue of Ueda and unpredictability were previous addressed in the Action, filed 4/16/2009.

The applicant further argues that the cited art teaches away from the claimed invention. Specifically, the applicant provides a limited interpretation of Yao which the applicant characterizes as "Yao is teaching that the preferred substitution size is 5

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amino acids" (Remarks, page 15). The teachings of Yao are not limited to a substitution of only 5 amino acids. Rather, Yao et al. teach "chimeric G_q protein variants comprise C-terminal sequences from transducin or $G_{\alpha_{olf}}$." (col.3, lines 10-13). Yao et al. teach that embodiments have "up to 44 amino acids of the C terminus of transducin or $G_{\alpha_{olf}}$ may be incorporated" (col.5, lines 22-23). In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples). Therefore, there is nothing in teachings of Yao, or the other cited art teaches away from the claimed structure of the chimeric G-protein comprising $G_{\alpha_{15}}$ or $G_{\alpha_{16}}$ wherein the 44 amino acid C-terminus of the $G_{\alpha_{15}}$ or $G_{\alpha_{16}}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2. Rather, the cited art suggests exactly the structure of the claimed products, having the C-terminal 44 amino acids. Therefore, the applicant finds the applicant's argument unpersuasive.

The applicant argues (remarks, pages 14-15) the specification teaches that the substitution of 44 amino acids from Gustducin into the C-terminus of $G_{\alpha_{15}}$ or $G_{\alpha_{16}}$ is a critical feature not recognized by the cited art, even though the applicant acknowledges that Yao et al. teach a range of substitutions from 5 to 44 that overlaps the instantly claimed chimeric G-protein. The applicant attempts to rebut the prima facie case of obviousness by citing the experiments of Ueda and contrasting them with the teachings of Yao (remarks, page 15). Contrary to the applicant's assertion, Yao specifically shows that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I).

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As Yao has provided an embodiment of a chimeric G-protein wherein the C terminus of the G_q-protein is replaced by 44 amino acids of transducin (col.5, lines 16-19 and 22-23), Yao has demonstrated the importance of this particular "tail length." Accordingly, Yao has demonstrated the criticality of the 44 amino acid substitution. Therefore, the applicant finds the applicant's argument unpersuasive.

The applicant seems to argue the unpredictability of generating a chimeric G-protein wherein the C terminus of the G-protein is replaced by 44 C-terminal amino acids of gustducin, based upon the unpredictableness of "modules," domains or homology at the C-termini of G-proteins associated with sensory receptors (remarks, pages 17-24). Despite all of the applicant's statements to the contrary, the cited art demonstrates that the C-termini of G-proteins associated with sensory receptors share common functionality between sensory receptors. For example, Margolskee teach "the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical. The carboxyl terminal identity is of particular importance because it encompasses the site that has been implicated in G protein/receptor interactions" (col.9, lines 13-16, emphasis added by examiner). Further, Margolskee teaches "among mammals...the α subunits of gustducin and the transducins comprise a subfamily of closely related proteins" (col.8, lines 66-67 and col.9, lines 1-2). In addition, Ruiz-Avila et al. seems to suggest both (1) the strong homology between gustducin and the transducins and (2) the importance of the C-terminus, "Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that

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of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors" (page 8870, col.1, Results). Therefore, the examiner concludes a skilled artisan based upon the knowledge in the art would understand that the 44 amino acid C-terminus of the G-proteins associated with sensory receptors is predictable in the art as having a similar function between these G-proteins. Therefore, the applicant finds the applicant's argument unpersuasive.

Accordingly, the examiner finds the applicant's claim amendments and arguments directed to the new claim amendments unpersuasive.

Therefore, the examiner hereby maintains the rejection of Claims 1, 6-13, and 18-34 under 35 U.S.C. 103(a) as being obvious over Margolskee (US-5,817,759, issued 6 October 1998) in view of Yao et al. (US-7,041,457, issued 9 May 2006) and further in view of Ruiz-Avila et al. (PNAS. July 17 2001. vol.98; No.15: 8868-8873).

The examiner reiterates the pending rejection below:

Claims 1, 6-13, 18-26 and 28-34 are rejected under 35 U.S.C. 103(a) as being obvious over Margolskee (US-5,817,759, issued 6 October 1998) in view of Yao et al. (US-7,041,457, issued 9 May 2006) and further in view of Ruiz-Avila et al. (PNAS. July 17 2001. vol.98; No.15: 8868-8873).

Claim 1 is directed to a chimeric G-protein comprising $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the 44 amino acid C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2, where the chimeric protein, when

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employed in a mammalian cell-based assay increases the signal strength to at least double the signal strength of wild type $G\alpha 16$.

Margolskee teaches “the α subunit of a novel taste receptor cell specific G protein, gustducin, or fragments and variants of the α subunit” (col. 3, lines 3-5). In addition, Margolskee teaches G-proteins which are $G_{\alpha 15}$ -Gustducin or $G_{\alpha 16}$ -Gustducin, of the subtypes of G-proteins, $G_{\alpha 15}$ and $G_{\alpha 16}$ (col.2, line 4). Margolskee teaches, “Gustducin α subunit variants...may comprise polypeptide analogs wherein one or more of the specified amino acids is deleted or replaced or wherein one or more nonspecified amino acids are added” (col.3, lines 48-51). Margolskee also teach “among mammals, a 1 to 3% difference in amino acids identity is typical among α isotypes, suggesting that the α subunits of gustducin and the transducins comprise a subfamily of closely related proteins” (col.8, lines 66-67 and col.9, lines 1-2). Margolskee “the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical. The carboxyl terminal identity is of particular importance because it encompasses the site that has been implicated in G protein/receptor interactions” (col.9, lines 13-16). In addition, Margolskee teach SEQ ID NO:3 which consists of the last 40 amino acids of Gustducin α subunit and is 100% identical to the last 40 of SEQ ID NO:2 of the instant application.

While Margolskee teach Gustducin α subunit variants and the importance of the carboxy 40 amino acids, Margolskee do not teach chimeric G-proteins comprising the carboxy 40 amino acids of Gustducin α subunit.

Yao et al. teach “chimeric G_q variants and the isolated nucleic acids encoding the same. In one embodiment, the chimeric G_q protein variants comprise C-terminal sequences from transducin or $G_{\alpha_{olf}}$.” (col.3, lines 10-13). Yao et al. teach that a preferred embodiment has “at least about five amino acids in the C terminus of the G_q -protein replace by at least about five amino acids from the C terminus of $G_{\alpha_{olf}}$ or transducin” (col.5, line 16-19) and “up to 44 amino acids of the C terminus of transducin or $G_{\alpha_{olf}}$ may be incorporated” (col.5, lines 22-23). Yao et al. indicated that the C-terminus of $G\alpha$ proteins can be modified to promote promiscuity of taste receptors. Yao et al. also describe the shared homologies of $G\alpha$ subunits. Further, Yao et al. also suggest that the gustducin-coupled bitter receptor can be modified to increase promiscuity with regard to GPCR coupling (col.4, lines 35-55). In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples).

Ruiz-Avila et al. teach “Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors” (page 8870, col.1, Results).

Consequently, claim 1 would be obvious, in light of the teachings of Margolskee and Yao et al. and Ruiz-Avila et al. The phrase, “when employed in a mammalian cell-based assay increases the signal strength to at least double the signal strength of wild type $G\alpha_{16}$,” does not further limit the structure of the claimed chimeric protein.

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Therefore, these are merely intrinsic characteristics of the claimed structure under certain manipulated conditions. MPEP 2112.01 indicates that "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Claims 6-9 are directed to nucleic acids encoding the claimed chimeric G-proteins, vectors comprising said nucleic acids, and cells comprising said vectors. The cited references are obvious over these limitations.

Claim 10 is directed to methods of producing a chimeric G-protein of claim 1 by recombinant technology. Margolskee teaches, "large scale production of gustducin α subunit polypeptides" by recombinant methods (col. 3, line 24-35). Margolskee teaches stably transformed host cells comprising the expression vector (col.3, line 24).

Claim 11 is directed to a method of analysis and discovery of modulators taste receptors of claim 12, wherein the taste receptors are bitter. Margolskee teaches, "methods for identifying taste modifying agents having the capability to affect interactions between the gustducin α subunit and taste receptors or effectors and also describes methods for utilizing such taste modifying agents to modify taste by mimicking or inhibiting...bitter." (col. 4, lines 52-56).

Claims 12-13 are directed to a methods of analysis and discovery of modulators of taste receptors which uses the chimeric G-protein of claim 1 in a mammalian cell-based assay. Margolskee teaches such mammalian cell-based assays that measure

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changes in intracellular messengers, including phosphodiesterase (col.13, lines 4-21) which affects Ca^{2+} and IP3 production.

Claim 18 is directed to a chimeric G-protein comprising $\text{G}_{\alpha 15}$ or $\text{G}_{\alpha 16}$ wherein the 44 amino acid C-terminus of the $\text{G}_{\alpha 15}$ or $\text{G}_{\alpha 16}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2, where the chimeric protein, when employed in a mammalian cell-based assay increases the signal strength to at least double the signal strength of wild type $\text{G}_{\alpha 16}$, wherein the resulting $\text{G}_{\alpha\text{q-Gust44}}$ chimeric G-protein has a sequence homology of at least 80% in the last 44 amino acids of SEQ ID NO: 2.

Margolskee teaches “the α subunit of a novel taste receptor cell specific G protein, gustducin, or fragments and variants of the α subunit” (col. 3, lines 3-5). Margolskee teaches, “Gustducin α subunit variants...may comprise polypeptide analogs wherein one or more of the specified amino acids is deleted or replaced or wherein one or more nonspecified amino acids are added” (col.3, lines 48-51). Margolskee also teach “among mammals, a 1 to 3% difference in amino acids identity is typical among α isotypes, suggesting that the α subunits of gustducin and the transducins comprise a subfamily of closely related proteins” (col.8, lines 66-67 and col.9, lines 1-2). Margolskee “the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical. The carboxyl terminal identity is of particular importance because it encompasses the site that has been implicated in G protein/receptor interactions” (col.9, lines 13-16). In addition, Margolskee teach SEQ ID NO:3 which consists of the last 40

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amino acids of Gustducin α subunit and is 100% identical to the last 40 amino acids of SEQ ID NO:2 of the instant application. Margolskee teaches, $G_{\alpha 15}$ and $G_{\alpha 16}$ (col.2, line 4). Margolskee teaches, "large scale production of gustducin α subunit polypeptides" by recombinant methods (col. 3, line 24-35). Margolskee teaches stably transformed host cells comprising the expression vector (col.3, line 24). Margolskee teaches, "methods for identifying taste modifying agents having the capability to affect interactions between the gustducin α subunit and taste receptors or effectors and also describes methods for utilizing such taste modifying agents to modify taste by mimicking or inhibiting...bitter." (col. 4, lines 52-56). Margolskee teaches such mammalian cell-based assays that measure changes in intracellular messengers, including phosphodiesterase (col.13, lines 4-21) which affects Ca^{2+} and IP3 production.

While Margolskee teach Gustducin α subunit variants and the importance of the carboxy 40 amino acids, Margolskee do not teach chimeric G-proteins comprising the carboxy 40 amino acids of Gustducin α subunit. Margolskee does not specifically teach the $G_{\alpha q}$ -Gustducin chimeric G-protein and also does not specifically recite replacement of the C-terminal sequence 44 amino acids of the gustducin receptor.

Yao et al. teach "chimeric G_q variants and the isolated nucleic acids encoding the same. In one embodiment, the chimeric G_q protein variants comprise C-terminal sequences from transducin or $G_{\alpha_{olf}}$." (col.3, lines 10-13). Yao et al. teach that a preferred embodiment has "at least about five amino acids in the C terminus of the G_q -protein replace by at least about five amino acids from the C terminus of $G_{\alpha_{olf}}$ or transducin" (col.5, line 16-19) and "up to 44 amino acids of the C terminus of transducin

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or $G\alpha_{olf}$ may be incorporated” (col.5, lines 22-23). Yao et al. indicated that the C-terminus of $G\alpha$ proteins can be modified to promote promiscuity of taste receptors. Yao et al. also describe the shared homologies of $G\alpha$ subunits. Further, Yao et al. also suggest that the gustducin-coupled bitter receptor can be modified to increase promiscuity with regard to GPCR coupling (col.4, lines 35-55). In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples).

Yao et al. teach, $G_{\alpha q}$ chimeric G-proteins (col.4, lines 12-27). In particular, the chimeric proteins described, combine various $G_{\alpha q}$ class proteins. Yao et al. also teach chimeric G-proteins that comprise C-terminal sequences from Transducin and $G\alpha_{olf}$ (col3, lines 12-13).

Yao et al. also teach analysis and discovery of agonists and antagonists of chemosensory receptors, using G_q -protein variants (col.3, lines 15-30), including the “gustducin-coupled bitter receptor” (col.4, line 53). Yao et al. further suggest that modulators could be used in “protein pharmaceutical and food industries” (col.4, line 32). Yao et al. teach that a preferred embodiment has “at least about five amino acids in the C terminus of the G_q -protein replace by at least about five amino acids from the C terminus of $G\alpha_{olf}$ or transducin” (col.5, line 16-19) and “up to 44 amino acids of the C terminus of transducin or $G\alpha_{olf}$ may be incorporated” (col.5, lines 22-23). Consequently, claims 3-4 would be obvious, in light of the teachings of Yao et al.

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While Yao et al. also teach chimeric G-proteins that comprise C-terminal sequences from Transducin and $G_{\alpha_{olf}}$ (col3, lines 12-13) and Yao et al. indicated that the C-terminus of G_{α} proteins can be modified to promote promiscuity of taste receptors, Yao et al. does not specifically teach a $G_{\alpha_q-Gustducin}$ chimeric G-protein having a C-terminal 44 amino acid substitution from Gustducin.

Ruiz-Avila et al. teach the nexus of gustducin and transducin homology and the importance of the C-terminus for interacting with taste receptors. Ruiz-Avila et al. teach “Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors” (page 8870, col.1, Results).

Consequently, all of the instant claims would be obvious, in light of the teachings of Margolskee and Yao et al. and Ruiz-Avila et al.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a G_{α_q} protein sequence are replaced with a 44 amino acid unit of Gustducin, where such 44 amino acid unit of Gustducin is the last 44 amino acids of Gustducin.

The person of ordinary skill in the art would have been motivated to make this protein because, “C-terminal substitution increases promiscuity of said variant G , protein as compared to the corresponding native G_q protein” (Yao et al. col.5, lines 20-22). While Yao et al. does not specifically teach making a chimera between G_q protein and gustducin, it is clearly obvious in light of the teachings involving substitutions with

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C-terminal sequences from other chemosensory molecules, transducin and $G_{\alpha_{olf}}$). In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples). Additionally, Margolskee teach that the carboxy terminal 40 amino acids of Gustducin are important for G protein/receptor interactions. Furthermore, Margolskee teach “the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical.” Ruiz-Avila et al. teach “Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors” (page 8870, col.1, Results). Furthermore, Yao et al. suggest that analysis and discovery of agonists and antagonists of chemosensory receptors, using G_q -protein variants can be performed using chimeric proteins and actually mention gustducin bitter receptor as a receptor which might be useful “to customize sensory perception” (col.4, line 32-33).

In addition, to the strong suggestion to make a G_{α_q} protein sequence are replaced with a 44 amino acid unit of Gustducin, where such 44 amino acid unit of Gustducin is the last 44 amino acids of Gustducin by the combined teachings of Margolskee in view of Yao et al. and further in view of Ruiz-Avila et al., there is another rationale for combining prior art elements according to known methods to yield predictable results. All of the claimed elements were known in the prior art and one

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skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (chimeric G_{α_q} -proteins and methods of using them; a suggestion of the importance of the c-terminal 44 amino acids of Gustducin and related G-proteins; knowledge that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors; and the knowledge that the C-terminus of $G\alpha$ proteins can be modified to promote promiscuity of taste receptors) are taught by Margolskee or Yao or Ruiz-Avila et al. It would be therefore predictably obvious to use a combination of these elements in a vaccine. The methods of using these chimeric G-proteins are further known in the art and are predictable; therefore they are likewise obvious.

An artisan would have expected success, because Yao et al. were successful in making similar chimeric G-proteins with other chemosensory receptors. Absent evidence to the contrary, there is no reason to believe that making a G_{α_q} protein sequence are replaced with a 44 amino acid unit of Gustducin, where such 44 amino acid unit of Gustducin is the last 44 amino acids of Gustducin would not be successful.

Therefore the products and methods as taught by Margolskee in view of Yao et al. and further in view of Ruiz-Avila et al. would have been *prima facie* obvious over the method of the instant application.

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NEW GROUNDS OF REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is directed to a chimeric G-protein comprising G_{α15} or G_{α16} wherein the 44 amino acid C-terminus of the G_{α15} or G_{α16} is replaced by the C-terminal 44 amino

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acids of Gustducin, described by SEQ ID NO:2, wherein the chimeric protein binds to one or more of the human bitter, sweet and umami taste receptors.

Margolskee teaches “the α subunit of a novel taste receptor cell specific G protein, gustducin, or fragments and variants of the α subunit” (col. 3, lines 3-5). In addition, Margolskee teaches G-proteins which are $G_{\alpha 15}$ -Gustducin or $G_{\alpha 16}$ -Gustducin, of the subtypes of G-proteins, $G_{\alpha 15}$ and $G_{\alpha 16}$ (col.2, line 4). Margolskee teaches, “Gustducin α subunit variants...may comprise polypeptide analogs wherein one or more of the specified amino acids is deleted or replaced or wherein one or more nonspecified amino acids are added” (col.3, lines 48-51). Margolskee also teach “among mammals, a 1 to 3% difference in amino acids identity is typical among α isotypes, suggesting that the α subunits of gustducin and the transducins comprise a subfamily of closely related proteins” (col.8, lines 66-67 and col.9, lines 1-2). Margolskee “the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical. The carboxyl terminal identity is of particular importance because it encompasses the site that has been implicated in G protein/receptor interactions” (col.9, lines 13-16). In addition, Margolskee teach SEQ ID NO:3 which consists of the last 40 amino acids of Gustducin α subunit and is 100% identical to the last 40 of SEQ ID NO:2 of the instant application.

While Margolskee teach Gustducin α subunit variants and the importance of the carboxy 40 amino acids, Margolskee do not teach chimeric G-proteins comprising the carboxy 40 amino acids of Gustducin α subunit.

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Yao et al. teach “chimeric G_q variants and the isolated nucleic acids encoding the same. In one embodiment, the chimeric G_q protein variants comprise C-terminal sequences from transducin or $G\alpha_{olf}$.” (col.3, lines 10-13). Yao et al. teach that a preferred embodiment has “at least about five amino acids in the C terminus of the G_q -protein replace by at least about five amino acids from the C terminus of $G\alpha_{olf}$ or transducin” (col.5, line 16-19) and “up to 44 amino acids of the C terminus of transducin or $G\alpha_{olf}$ may be incorporated” (col.5, lines 22-23). Yao et al. indicated that the C-terminus of $G\alpha$ proteins can be modified to promote promiscuity of taste receptors. Yao et al. also describe the shared homologies of $G\alpha$ subunits. Further, Yao et al. also suggest that the gustducin-coupled bitter receptor can be modified to increase promiscuity with regard to GPCR coupling (col.4, lines 35-55). In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples).

Ruiz-Avila et al. teach “Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors” (page 8870, col.1, Results).

Consequently, claim 37 would be obvious, in light of the teachings of Margolskee and Yao et al. and Ruiz-Avila et al. The claim amendments directed to binding taste receptors do not further limit the structure of the claimed chimeric protein. Therefore, these are merely intrinsic characteristics of the claimed protein structure. MPEP

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2112.01 indicates that "Where the claimed and prior art products are identical or substantially identical in structure... a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). However, even though this limitation need not be met, the cited art teaches that the chimeric G-protein comprising $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the 44 amino acid C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2 binds at least the bitter taste receptors (Yao, col.4, line 32-33; Margolskee, col. 4, lines 52-56).

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to make a chimeric G-protein comprising $G_{\alpha 15}$ or $G_{\alpha 16}$ wherein the 44 amino acid C-terminus of the $G_{\alpha 15}$ or $G_{\alpha 16}$ is replaced by the C-terminal 44 amino acids of Gustducin, described by SEQ ID NO:2, The person of ordinary skill in the art would have been motivated to make this protein because, "C-terminal substitution increases promiscuity of said variant G, protein as compared to the corresponding native G_q protein" (Yao et al. col.5, lines 20-22). While Yao et al. does not specifically teach making a chimera between G_q protein and gustducin, it is clearly obvious in light of the teachings involving substitutions with C-terminal sequences from other chemosensory molecules, transducin and $G_{\alpha_{olf}}$. In particular, Yao et al. show that their chimeric G-protein wherein the C terminus of the G_q -protein is replaced by 44 amino acids of transducin has functional activity with the Taste Receptor (col.8, Table I, and Examples). Additionally, Margolskee teach that the carboxy terminal 40 amino acids of Gustducin are important for G protein/receptor interactions. Furthermore, Margolskee

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teach “the carboxy terminal 60 amino acids of all three proteins [gustducin and rod and cone transducins] are highly conserved, while the carboxyl terminal 38 amino acids are identical.” Ruiz-Avila et al. teach “Several biochemical studies suggest that the interaction of gustducin with its cognate taste receptors is similar to that of transducin with rhodopsin. A key result of these studies is that the C terminus of α -gustducin is a critical determinant for its interaction with taste receptors” (page 8870, col.1, Results). Furthermore, Yao et al. suggest that analysis and discovery of agonists and antagonists of chemosensory receptors, using G_q -protein variants can be performed using chimeric proteins and actually mention gustducin bitter receptor as a receptor which might be useful “to customize sensory perception” (col.4, line 32-33).

In addition, to the strong suggestion to make a $G_{\alpha q}$ protein sequence are replaced with a 44 amino acid unit of Gustducin, where such 44 amino acid unit of Gustducin is the last 44 amino acids of Gustducin by the combined teachings of Margolskee in view of Yao et al. and further in view of Ruiz-Avila et al., there is another rationale for combining prior art elements according to known methods to yield predictable results. All of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (chimeric $G_{\alpha q}$ -proteins and methods of using them; a suggestion of the importance of the c-terminal 44 amino acids of Gustducin and related G-proteins; knowledge that the C terminus of α -gustducin is a critical determinant for its interaction

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with taste receptors; and the knowledge that the C-terminus of G α proteins can be modified to promote promiscuity of taste receptors) are taught by Margolskee or Yao or Ruiz-Avila et al. It would be therefore predictably obvious to use a combination of these elements in a vaccine. The methods of using these chimeric G-proteins are further known in the art and are predictable; therefore they are likewise obvious.

An artisan would have expected success, because Yao et al. were successful in making similar chimeric G-proteins with other chemosensory receptors. Absent evidence to the contrary, there is no reason to believe that making a G α_q protein sequence are replaced with a 44 amino acid unit of Gustducin, where such 44 amino acid unit of Gustducin is the last 44 amino acids of Gustducin would not be successful.

Therefore the products and methods as taught by Margolskee in view of Yao et al. and further in view of Ruiz-Avila et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633